Title

Racial/ethnic disparities in hepatocellular carcinoma treatment and survival in California, 1988-2012.

Journal

World journal of gastroenterology, 22(38)

ISSN

1007-9327

Authors

Stewart, Susan L
Kwong, Sandy L
Bowlus, Christopher L
et al.

Publication Date

2016-10-01

DOI

10.3748/wjg.v22.i38.8584

Peer reviewed

World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v22.i38.8584

World J Gastroenterol 2016 October 14; 22(38): 8584-8595
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Observational Study

Racial/ethnic disparities in hepatocellular carcinoma treatment and survival in California, 1988-2012

Susan L Stewart, Sandy L Kwong, Christopher L Bowlus, Tung T Nguyen, Annette E Maxwell, Roshan Bastani, Eric W Chak, Moon S Chen Jr

Susan L Stewart, Division of Biostatistics, Department of Public Health Sciences, University of California, Davis School of Medicine, Sacramento, CA 95817, United States

Sandy L Kwong, California Department of Public Health, Sacramento, CA 95817, United States

Christopher L Bowlus, Tung Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of California, Davis School of Medicine, Sacramento, CA 95817, United States

Tung T Nguyen, Eric W Chak, Division of General Internal Medicine, University of California, San Francisco, CA 94101, United States

Annette E Maxwell, Roshan Bastani, UCLA Kaiser Permanente Center for Health Equity, Fielding School of Public Health and Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA 90095, United States

Moon S Chen Jr, Division of Hematology and Oncology, Department of Internal Medicine, University of California, Davis School of Medicine, Sacramento, CA 95817, United States

Moon S Chen Jr, Cancer Control/Cancer Health Disparities, University of California, Davis Comprehensive Cancer Center, Sacramento, CA 95817, United States

Author contributions: All authors contributed to the manuscript.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

Correspondence to: Moon S Chen Jr, PhD, MPH., Professor, Associate Director, Cancer Control/Cancer Health Disparities, University of California, Davis Comprehensive Cancer Center, 2450 48th Street, Suite 1600, Sacramento, CA 95817, United States.
mschenjr@ucdavis.edu
Telephone: +1-916-7345800

Received: June 28, 2016
Peer-review started: June 28, 2016
First decision: July 29, 2016
Revised: August 16, 2016
Accepted: September 12, 2016
Article in press: September 12, 2016
Published online: October 14, 2016

Abstract

AIM

To describe racial/ethnic differences in treatment and survival among liver cancer patients in a population-based cancer registry.

METHODS

Invasive cases of primary hepatocellular carcinoma, *n* = 33270, diagnosed between January 1, 1988-December 31, 2012 and reported to the California Cancer Registry were analyzed by race/ethnicity, age, gender, geographical region, socio-economic status, time period of diagnosis, stage, surgical treatment, and survival. Patients were classified into 15 racial/ethnic groups: non-Hispanic White (White, *n* = 12710), Hispanic (*n* = 8500), Chinese (*n* = 2723), non-Hispanic Black (Black, *n* = 2609), Vietnamese (*n* = 2063), Filipino (*n* = 1479), Korean (*n* = 1099), Japanese (*n* = 658), American Indian/Alaskan Native (AIAN, *n* = 281), Laotian/Hmong

(*n* = 244), Cambodian (*n* = 233), South Asian (*n* = 190), Hawai`ian/Pacific Islander (*n* = 172), Thai (*n* = 95), and Other Asian (*n* = 214). The main outcome measures were receipt of surgical treatment, and cause-specific and all-cause mortality.

RESULTS

After adjustment for socio-demographic characteristics, time period, and stage of disease, compared to Whites, Laotian/Hmong [odds ratio (OR) = 0.30, 95%CI: 0.17-0.53], Cambodian (OR = 0.65, 95%CI: 0.45-0.96), AIAN (OR = 0.66, 95%CI: 0.46-0.93), Black (OR = 0.76, 95%CI: 0.67-0.86), and Hispanic (OR = 0.78, 95%CI: 0.72-0.84) patients were less likely, whereas Chinese (OR = 1.58, 95%CI: 1.42-1.77), Koreans (OR = 1.45, 95%CI: 1.24-1.70), Japanese (OR = 1.41, 95%CI: 1.15-1.72), and Vietnamese (OR = 1.26, 95%CI: 1.12-1.42) were more likely to receive surgical treatment. After adjustment for the same covariates and treatment, cause-specific mortality was higher for Laotian/Hmong [(hazard ratio (HR) = 1.50, 95%CI: 1.29-1.73)], Cambodians (HR = 1.35, 95%CI: 1.16-1.58), and Blacks (HR = 1.07, 95%CI: 1.01-1.13), and lower for Chinese (HR = 0.82, 95%CI: 0.77-0.86), Filipinos (HR = 0.84, 95%CI: 0.78-0.90), Vietnamese (HR = 0.85, 95%CI: 0.80-0.90), Koreans (HR = 0.90, 95%CI: 0.83-0.97), and Hispanics (HR = 0.91, 95%CI: 0.88-0.94); results were similar for all-cause mortality.

CONCLUSION

Disaggregated data revealed substantial racial/ethnic differences in liver cancer treatment and survival, demonstrating the need for development of targeted interventions to mitigate disparities.

Key words: Disparities; Treatment; Survival; Liver cancer; Hepatocellular carcinoma

Core tip: We found substantial racial/ethnic differences in treatment and survival in our analysis of 33270 cases of hepatocellular carcinoma from the world's largest cancer registry in a single geo-political jurisdiction, diagnosed over a 25-year period and disaggregated into 15 racial/ethnic categories. Such granularity provides more precise identification of populations at risk by race/ethnicity, age, gender, socio-economic status, and stage of disease so that targeted interventions to mitigate disparities can be developed.

Stewart SL, Kwong SL, Bowlus CL, Nguyen TT, Maxwell AE, Bastani R, Chak EW, Chen MS Jr. Racial/ethnic disparities in hepatocellular carcinoma treatment and survival in California, 1988-2012. *World J Gastroenterol* 2016; 22(38): 8584-8595 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i38/8584.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i38.8584

INTRODUCTION

Cancer of the liver and intrahepatic bile duct, of which approximately 80% is hepatocellular carcinoma (HCC)[1], led the 17 most common cancer sites with a 3.1% average annual increase in mortality rates between 2008 and 2012 among both men and women in the United States[2]. In contrast, mortality rates declined an average of 1.8% per year among men and 1.4% among women during the same time period for all cancer sites combined[2]. HCC's prominence is further exemplified by the quadrupling of its incidence from 1.5 to 6.2 per 100000 between 1973 and 2011[3]. Worldwide, liver cancer has become the second leading cause of cancer deaths[4].

The principal risk factors for HCC are chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections[5]. After tobacco use, HBV infection, because of its etiological linkage to liver cancer, is the next most important cause of cancer worldwide[6,7]. HCV-related HCC has become the fastest increasing cause of cancer mortality in the United States[8]. In addition to alcohol consumption[8], other risk factors contributing to the increase in HCC in the United States are metabolic syndrome including diabetes[9,10] and obesity[8], which are risk factors for non-alcoholic steatohepatitis (NASH)[11]. There is evidence that the peak of the HCC epidemic may be near[3,12]. However, because HCC disproportionately affects populations of color[2]-African Americans, American Indians/Alaska Natives, Asian Americans, Hispanics, and Pacific Islanders-and because many of these racial/ethnic populations are increasing at faster rates than the population as a whole, the burden of liver cancer will continue to increase[2,13,14] unless detected earlier and properly treated or prevented[15].

Although the 5-year relative survival rate for liver cancer has risen in recent years, from 3.4% in 1975-77 to 18.1% in 2006-2012[16], it remains lower than that of most other common cancers[16]. Treatments have become more effective[11], and a larger proportion of patients are being diagnosed with early stage disease[17]. However not all HCC patients have benefited from these improvements[18]; consequently, racial/ethnic, socioeconomic, and geographic disparities in mortality persist[12,17].

Previous analyses of HCC survival and treatment characteristics have typically reported on HCC cases aggregated by ethnicity (Hispanic or non-Hispanic) accompanied by broad racial categories, *e.g.*, American Indian/Alaska Native, Asian, Black, Native Hawaiian and Other Pacific Islander[19-21], or focused on Black-White comparisons[22]. Our previous study of more than 6000 HCC cases diagnosed in California in 1988-2007, which reported on specific Asian ethnicities, found substantial inter-ethnic variation in survival but did not include comparison with other racial/ethnic groups[23]. Rarely have HCC survival and

treatment characteristics been characterized for 15 race/ethnic groups in a large geographically contiguous area over a period of 25 years.

The purpose of this study was to identify disparities in treatment and survival by race and ethnicity among more than 33000 California residents diagnosed with HCC from 1988-2012, and determine the extent to which variables such as age, gender, stage at diagnosis, and socioeconomic status explain these disparities.

MATERIALS AND METHODS

The data source for our study is the California Cancer Registry (CCR), the world's largest population-based registry with ethnic-specific data in a single contiguous political jurisdiction. The CCR covers the entire state of California and includes three Surveillance, Epidemiology, and End Results (SEER) regions: the Greater Bay Area, Los Angeles County, and Greater California. The CCR has achieved the highest standards for cancer registry quality established by the North American Association of Central Cancer Registries (NAACCR) and the National Program of Cancer Registries (NPCR) for completeness and quality. Reporting of cancer cases to the CCR has been legislatively mandated in California since 1985. The CCR includes data from all cancer cases (except basal and squamous cell carcinoma of the skin and carcinoma *in situ* of the cervix), and its completeness is estimated to be 95% or greater.

The CCR follows standardized data collection and quality-control procedures in terms of racial/ethnic categorizations and cancer diagnoses[24]. Race/ethnicity information for the HCC cases is primarily based on information contained in the patient's medical record. This information may be based on self-identification by the patient, on the assumptions by an admissions clerk or other medical personnel, or by inference using race/ethnicity of parents, birthplace, maiden name, or last name. To better identify Hispanics and Asian ethnic groups, cases were run through NAACCR Hispanic and Asian Identification Algorithm[25,26]. Cases are classified as non-Hispanic White (White), non-Hispanic Black (Black), Hispanic, American Indian/Alaskan Native, Asian American, and Native Hawaiian/Pacific Islander. Asian race is further divided into twelve groups, the nine largest in California in rank order according to their 2010 U.S. Census populations are as follows: Filipino, Chinese (including Taiwanese), Vietnamese, South Asian (Asian Indian, Pakistani, Bangladeshi, Sri Lankan), Korean, Japanese, Hmong and Laotian, Cambodian, and Thai.

In our study, Laotian and Hmong have been combined into one group because the majority of foreign-born Hmong were born in Laos[27], and older Hmong individuals may classify themselves as Laotian because they were formerly citizens of Laos[28]. South Asians, whose land of origin is the Indian subcontinent[29,30], are comprised of Asian Indian, Pakistani, other South Asian, Bangladeshi, Bhutanese, Nepalese, Sikh, and Sri Lankan. We combined cases from smaller or unknown Asian ethnic groups into an Other Asian category. Excluded from our analyses were 107 HCC cases with unknown race.

The analysis included all invasive hepatocellular carcinoma (HCC) cases diagnosed between January 1, 1988 and December 31, 2012 and reported to the CCR as of December 2015. We used the *International Classification of Diseases for Oncology, Third Edition* site code (C22.0) and histology code (8170) to identify patients with HCC among all patients with primary liver cancer. Eligibility was restricted to HCC as the first primary cancer in order to eliminate survival differences due to the effects of other cancers. Only cases with diagnostic confirmation of HCC were included in our study (92.3%). Diagnostic confirmation of HCC was defined as having positive histology (56.7%), positive radiological test (27.6%), cytology (11.2%), laboratory test/marker study (4.2%), or direct visualization (0.3%). A total of 33270 invasive HCC cases that met the above requirements were analyzed for this study.

Patient vital status was updated using both passive and active follow-up methods. Passive follow-up methods included annual record linkages with the California State death file, National Death Index, Social Security Death Master File, Medicare and Medicaid, California Department of Motor Vehicles, Voter Registration, and National Change of Address. Active follow-up methods required contacting physician's offices, hospitals, patient's relatives, and patients. The follow-up period for this study began at HCC diagnosis and ended at the earlier of the date of death or last follow-up and December 31, 2013 (the end of the latest full year of case follow-up at the time these data were reported).

Statistical analysis

We used χ^2 tests to examine bivariate relationships between race/ethnic groups and the variables displayed in Table 1. These variables included time period of diagnosis divided into five consecutive five-year intervals; age at diagnosis (< 50, 50-59, 60-69, 70-79, and 80 years or older); gender; geographical region (Los Angeles County, Greater San Francisco Bay Area, Central California, Northern California, and San Diego-Imperial-Orange Counties); stage of diagnosis (remote, regional, local, and unstaged); type of surgery (none, local, resection/transplant); and socioeconomic status (SES) on the basis of neighborhood income levels in quintiles. In categorizing type of surgery, resection and transplant were combined because SEER did not begin coding transplantation as a separate category until 1998.

Individual patient-level SES data are not collected by the CCR, and neighborhood SES was calculated using two methods. For cases diagnosed from 1988 through 2005, the index of SES was a composite

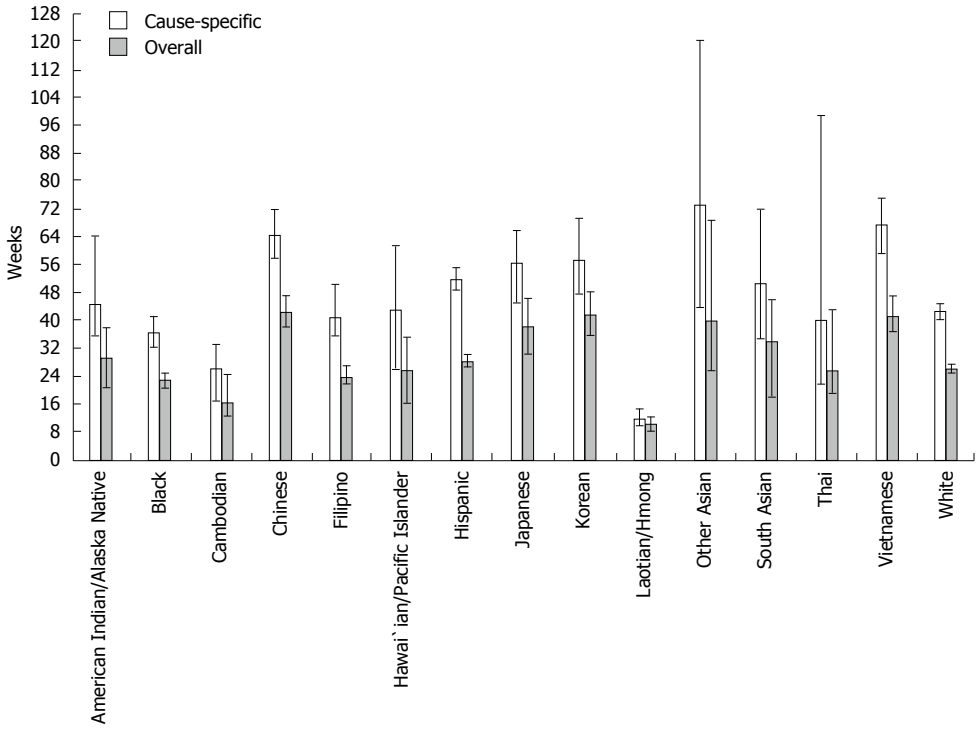

Figure 1 Median survival for patients with hepatocellular carcinoma by race/ethnicity in California, 1988-2012. Note: Error bars are limits of 95%CI.

variable created by principal components analysis using a number of variables from 1990 and 2000 Census data at the block group level. The Census variables used in creating the aggregate SES measure included: education index, median household income, proportion below 200% of the poverty level, median rent, median house value, proportion with a blue collar job, and proportion older than 16 in the workforce without a job. Block group quintiles based on statewide measurement of the SES variable were used in the analysis[31]. For cases diagnosed from 2006 through 2012, a composite variable was also created by principal components analysis using variables from the American Community Survey (ACS) at the block group level. The index used the following variables: education index, percent persons with a ratio of household income to poverty line 2 or higher (percent persons above 200% poverty line), percent persons with a blue collar job, percent persons employed, median rental, median value of owner-occupied housing unit, and median household income. The SES index could not be calculated if any of the seven components were missing. Missing values were imputed using multiple imputation, and the SES index was based on the imputed data[32].

The main difference between the two SES indexes is that the index based on the ACS used the inverse complement of two variables used from the 2000 Census: percent unemployed (2000 Census) and percent less than 200% of poverty line (ACS). Cases missing Census block group due to incomplete address at time of diagnosis (4.9% of patients) were randomly allocated to census block groups within county of residence because excluding these cases has been shown to bias results. Each case was assigned a neighborhood SES quintile, based on the distribution of SES across census block groups in California.

Logistic regression was used to evaluate the association between race/ethnicity and receipt of surgical treatment (any *vs* none) before and after adjustment for time period of diagnosis, age, gender, geographic region, SES quintile, and stage at diagnosis; because prioritization for transplantation for HCC changed in 2002[33], we included an interaction between time period and stage in the multivariable model, allowing estimation of stage effects for each time period and time period effects at the referent level of stage. Odds ratios (OR) and 95%CI are shown in Table 2.

Kaplan-Meier methods were used to estimate cause-specific and overall survival curves for each of the race/ethnic groups, and the log-rank test was used to assess racial/ethnic differences in survival. Median survival times with 95%CI are presented in Figure 1. Cox proportional hazards models were used to evaluate the association between race/ethnicity and survival, before and after adjustment for the effects of time period of diagnosis, age, gender, geographic region, SES quintile, stage at diagnosis, and type of surgery. Both cause-specific and all cause hazard ratios were calculated. Using non-Hispanic White as the referent group, hazard ratios (HR) and 95%CI were calculated for death from HCC. Survival time was measured in weeks from the date of diagnosis to death or censoring. People who were still alive on December 31, 2013 were censored

Table 1 Demographic and tumor characteristics by race/ethnic groups among patients with hepatocellular carcinoma in California, 1988-2012 (*n* = 33270)

	American Indian/ Alaska Native (*n* = 281)		Black (*n* = 2609)		Cambodian (*n* = 233)		Chinese (*n* = 2723)		Filipino (*n* = 1479)		Hawai`ian/ Pacific Islander (*n* = 172)		Hispanic (*n* = 8500)		Japanese (*n* = 658)		Korean (*n* = 1099)		Laotian/ Hmong (*n* = 244)		Other Asian (*n* = 214)		South Asian (*n* = 190)		Thai (*n* = 95)		Vietnamese (*n* = 2063)		White (*n* = 12710)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Age at diagnosis																														
< 50	47	16.7	323	12.4	63	27.0	437	16.0	219	14.8	30	17.4	1170	13.8	30	4.6	172	15.7	65	26.6	44	20.6	13	6.8	29	30.5	326	15.8	1181	9.3
50-59	102	36.3	936	35.9	78	33.5	579	21.3	324	21.9	58	33.7	2604	30.6	116	17.6	284	25.8	62	25.4	58	27.1	44	23.2	27	28.4	533	25.8	3705	29.2
60-69	90	32.0	833	31.9	57	24.5	744	27.3	339	22.9	46	26.7	2424	28.5	219	33.3	346	31.5	72	29.5	59	27.6	65	34.2	22	23.2	596	28.9	3640	28.6
70-79	34	12.1	391	15.0	19	8.2	689	25.3	403	27.2	30	17.4	1657	19.5	206	31.3	233	21.2	31	12.7	44	20.6	45	23.7	13	13.7	471	22.8	2831	22.3
⩾ 80	8	2.8	126	4.8	16	6.9	274	10.1	194	13.1	8	4.7	645	7.6	87	13.2	64	5.8	14	5.7	9	4.2	23	12.1	-[1]	-[1]	137	6.6	1353	10.6
Gender																														
Male	214	76.2	1971	75.6	182	78.1	2078	76.3	1111	75.1	138	80.2	6368	74.9	285	43.3	761	69.2	188	77.0	155	72.4	138	72.6	73	76.8	1622	78.6	9762	76.8
Female	67	23.8	638	24.4	51	21.9	645	23.7	368	24.9	34	19.8	2132	25.1	373	56.7	338	30.8	56	23.0	59	27.6	52	27.4	22	23.2	441	21.4	2948	23.2
Socioeconomic status (SES)																														
1 - Low SES	75	26.7	867	33.2	113	48.5	377	13.8	204	13.8	30	17.4	2975	35.0	49	7.4	176	16.0	129	52.9	31	14.5	13	6.8	12	12.6	316	15.3	1599	12.6
2	82	29.2	586	24.8	42	18.0	428	15.7	286	19.3	42	24.4	2248	26.4	118	17.9	184	16.7	68	27.9	38	17.8	32	16.8	31	32.6	541	26.2	2512	19.8
3	72	25.6	483	18.5	33	14.2	488	17.9	367	24.8	40	23.3	1621	19.1	153	23.3	188	17.1	26	10.7	42	19.6	38	20.0	20	21.1	481	23.3	2977	23.4
4	36	12.8	409	15.7	26	11.2	660	24.2	402	27.2	34	19.8	1054	12.4	164	24.9	255	23.2	19	7.8	63	29.4	60	31.6	18	18.9	400	19.4	2942	23.1
5 - High SES	16	5.7	203	7.8	19	8.2	770	28.3	220	14.9	26	15.1	602	7.1	174	26.4	296	26.9	-[1]	-[1]	40	18.7	47	24.7	14	14.7	325	15.8	2680	21.1
Region																														
San Francisco-Oakland	44	15.7	753	28.9	31	13.3	1482	54.4	517	35.0	62	36.0	1329	15.6	171	26.0	178	16.2	28	11.5	79	36.9	57	30.0	14	14.7	701	34.0	2637	20.7
Central California	78	27.8	335	12.8	24	10.3	78	2.9	109	7.4	21	12.2	2129	25.0	65	9.9	67	6.1	75	30.7	39	18.2	36	18.9	11	11.6	104	5.0	2705	21.3
Northern California	100	35.6	323	12.4	38	16.3	152	5.6	126	8.5	22	12.8	635	7.5	92	14.0	34	3.1	85	34.8	13	6.1	40	21.1	7	7.4	116	5.6	2578	20.3
San Diego-Imperial-Orange	33	11.7	206	7.9	22	9.4	173	6.4	263	17.8	28	16.3	1258	14.8	112	17.0	197	17.9	43	17.6	19	8.9	29	15.3	8	8.4	760	36.8	2208	17.4
Los Angeles	26	9.3	992	38.0	118	50.6	838	30.8	464	31.4	39	22.7	3149	37.0	218	33.1	623	56.7	13	5.3	64	29.9	28	14.7	55	57.9	382	18.5	2582	20.3
Stage at diagnosis																														
Local	109	38.8	987	37.8	96	41.2	1179	43.3	584	39.5	73	42.4	3825	45.0	288	43.8	450	40.9	71	29.1	102	47.7	84	44.2	38	40.0	947	45.9	5355	42.1
Regional	85	30.2	668	25.6	61	26.2	606	22.3	384	26.0	43	25.0	2010	23.6	142	21.6	267	24.3	52	21.3	48	22.4	53	27.9	22	23.2	498	24.1	2988	23.5
Remote	62	22.1	682	26.1	55	23.6	645	23.7	362	24.5	44	25.6	1812	21.3	149	22.6	242	22.0	88	36.1	49	22.9	40	21.1	24	25.3	437	21.2	2905	22.9
Unstaged	25	8.9	272	10.4	21	9.0	293	10.8	149	10.1	12	7.0	853	10.0	79	12.0	140	12.7	33	13.5	15	7.0	13	6.8	11	11.6	181	8.8	1462	11.5
Time period of diagnosis																														
1988-1992	9	3.2	217	8.3	22	9.4	334	12.3	161	10.9	14	8.1	557	6.6	84	12.8	114	10.4	29	11.9	9	4.2	12	6.3	7	7.4	128	6.2	1257	9.9
1993-1997	14	5.0	319	12.2	30	12.9	435	16.0	195	13.2	25	14.5	809	9.5	108	16.4	178	16.2	41	16.8	11	5.1	15	7.9	12	12.6	271	13.1	1681	13.2
1998-2002	49	17.4	472	18.1	45	19.3	543	19.9	304	20.6	32	18.6	1461	17.2	139	21.1	267	24.3	56	23.0	51	23.8	29	15.3	21	22.1	429	20.8	2252	17.7
2003-2007	88	31.3	683	26.2	61	26.2	695	25.5	408	27.6	41	23.8	2340	27.5	166	25.2	270	24.6	49	20.1	50	23.4	61	32.1	16	16.8	575	27.9	3208	25.2
2008-2012	121	43.1	918	35.2	75	32.2	716	26.3	411	27.8	60	34.9	3333	39.2	161	24.5	270	24.6	69	28.3	93	43.5	73	38.4	39	41.1	660	32.0	4312	33.9
Type of surgery																														
None	238	84.7	2214	84.9	198	85.0	2007	73.7	1220	82.5	138	80.2	7062	83.1	491	74.6	805	73.2	230	94.3	158	73.8	145	76.3	75	78.9	1536	74.4	10117	79.6
Local	20	7.1	150	5.7	13	5.6	184	6.8	60	4.1	10	5.8	550	6.5	58	8.8	83	7.6	7	2.9	16	7.5	18	9.5	-[1]	-[1]	194	9.4	925	7.3
Resection/transplant	23	8.2	245	9.4	22	9.4	532	19.5	199	13.5	24	14.0	888	10.4	109	16.6	211	19.2	7	2.9	40	18.7	27	14.2	16	16.8	333	16.1	1668	13.1

[1]Less than 5 cases. χ^2, $P < 0.0001$ for racial/ethnic differences in all variables tabulated.

on that date; in cause-specific survival analyses, because the outcome of interest was death due to HCC, people who died of other causes before that date were censored at date of death. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC); statistical significance was assessed at the 0.05 level (2-sided).

RESULTS

Patient characteristics

A total of 33270 patients in the designated race/ethnic groups were diagnosed with HCC in California in 1988-2012 and reported to the CCR as of December 31, 2015. The largest number were identified as non-Hispanic White (n = 12710), followed by Hispanic (n = 8500), Chinese (n = 2723), non-Hispanic Black (n = 2609), Vietnamese (n = 2063), Filipino (n = 1479), and Korean (n = 1099). As shown in Table 1, the distributions of all patient characteristics differed significantly by race ethnicity (P < 0.0001). There was a male predominance of cases in all groups (69%-80%), except Japanese (43%). Overall, 12% were under age 50 at diagnosis, with highest proportions under 50 among Thai (31%), Cambodians (27%), and Laotian/Hmong (27%). There were substantial disparities in SES: those most likely to live in lowest quintile neighborhoods were Laotian/Hmong (53%), Cambodians (48%), Hispanics (35%), and Blacks (33%). There were also disparities in stage at diagnosis and receipt of treatment. Those least likely to be diagnosed with local stage tumors (43% overall) were Laotian/Hmong (29%), Blacks (38%), AIANs (39%), and Filipinos (39%). Those least likely to receive a resection or transplant (13% overall) were Laotian/Hmong (3%), AIANs (8%), Blacks (9%), and Cambodians (9%).

Receipt of surgical treatment

Compared to Whites, Laotian/Hmong (OR = 0.24, 95%CI: 0.14-0.41), Cambodians (OR = 0.69, 95%CI: 0.48-0.99), Blacks (OR = 0.70, 95%CI: 0.62-0.78), AIAN (OR = 0.71, 95%CI: 0.51-0.98), Hispanics (OR = 0.79, 95%CI: 0.74-0.85), and Filipinos (OR = 0.83, 95%CI: 0.72-0.95) were less likely, and Koreans (OR = 1.43, 95%CI: 1.24-1.64), Chinese (OR = 1.39, 95%CI: 1.27-1.53), Other Asians (OR = 1.38, 95%CI: 1.02-1.88), Vietnamese (OR = 1.34, 95%CI:1.20-1.49), and Japanese (OR = 1.33, 95%CI: 1.11-1.59) were more likely to receive surgical treatment (Table 2). After adjustment for demographic characteristics, time period, and stage of disease, Laotian/Hmong (OR = 0.30, 95%CI: 0.17-0.53), Cambodian (OR = 0.65, 95%CI: 0.45-0.96), AIAN (OR = 0.66, 95%CI: 0.46-0.93), Black (OR = 0.76, 95%CI: 0.67-0.86), and Hispanic (OR=0.78, 95%CI 0.72-0.84) patients were less likely, whereas Chinese (OR = 1.58, 95%CI:1.42-1.77), Koreans (OR = 1.45, 95%CI: 1.24-1.70), Japanese (OR = 1.41, 95%CI: 1.15-1.72), and Vietnamese (OR = 1.26, 95%CI: 1.12-1.42) were more likely to receive surgical treatment. The odds of treatment decreased with age (over 80 *vs* under 50: OR = 0.20, 95%CI: 0.17-0.24) and increased with SES (highest vs. lowest quintile: OR = 1.84, 95%CI: 1.66-2.05); males were less likely than females to be treated (OR = 0.82, 95%CI: 0.77-0.88). The time X stage interaction was statistically significant (P = 0.0014): patients with local stage disease had a greater advantage over those with remote stage disease in 2003-2012 (ORs = 13.0 and 13.6) than in 1988-2002 (ORs = 8.28, 8.81, and 8.07).

Survival

Kaplan-Meier analysis: Both cause-specific and overall survival differed significantly by race/ethnicity (log-rank P < 0.0001). Cause-specific median survival in weeks (Figure 1) was lowest for Laotian/Hmong (11.6, 95%CI: 9.6-14.4), followed by Cambodians (26.1, 95%CI: 16.7-33.1), Blacks (36.3, 95%CI: 32.1-41.0), Thai (39.9, 95%CI: 21.7-98.7), Filipinos (41.0, 95%CI: 35.4-50.0), Whites (42.4, 95%CI: 40.1-44.6), Hawai`ians/Pacific Islanders (42.7, 95%CI: 25.7-61.4), AIANs [44.6, 95%CI: (35.6-64.1)], South Asians (50.6, 95%CI: 34.4-72.0), Hispanics (51.9, 95%CI: 48.4-55.3), Japanese (56.3, 95%CI: 44.9-65.9), Koreans (57.4, 95%CI: 47.6-69.4), Chinese (64.4, 95%CI: 57.7-71.7), Vietnamese (67.3, 95%CI: 59.1-75.0), and Other Asians (73.3, 95%CI: 43.7-120.3). Results were similar for all cause survival.

Cox proportional hazards models: Compared to Whites, higher cause-specific mortality was experienced by Laotian/Hmong [hazard ratio (HR) = 1.91, 95%CI: 1.65-2.21], Cambodians (HR = 1.38, 95%CI: 1.18-1.60), and Blacks (HR = 1.12, 95%CI: 1.06-1.18), and lower mortality by Other Asians (HR = 0.80, 95%CI 0.67-0.96), Chinese (HR = 0.81, 95%CI: 0.77-0.86), Vietnamese (HR = 0.83, 95%CI: 0.79-0.89), Koreans (HR = 0.87, 95%CI: 0.80-0.93), and Hispanics (HR = 0.91, 95%CI: 0.88-0.95) (Table 3). After adjustment for demographics, time period, stage of disease, and treatment, mortality remained higher for Laotian/Hmong (HR = 1.50, 95%CI: 1.29-1.73), Cambodians (HR = 1.35, 95%CI: 1.16-1.58), and Blacks (HR = 1.07, 95%CI: 1.01-1.13), and was lower for Chinese (HR = 0.82, 95%CI: 0.77-0.86), Filipinos (HR = 0.84, 95%CI: 0.78-0.90), Vietnamese (HR = 0.85, 95%CI: 0.80-0.90), Koreans (HR = 0.90, 95%CI: 0.83-0.97), and Hispanics (HR = 0.91, 9 95%CI: 0.88-0.94). Lower mortality was associated with younger age, female gender, earlier stage disease, receipt of surgical treatment, higher SES, and later time period of diagnosis. Results were similar for all-cause mortality.

Table 2 Factors associated with receipt of surgical treatment for hepatocellular carcinoma in California, 1988-2012 (n = 33270)

	Receipt of surgical treatment			
	Unadjusted OR	95%CI	Adjusted[1] OR	95%CI
American Indian/Alaska Native	0.71[a]	0.51-0.98[a]	0.66[a]	0.46-0.93[a]
Black	0.70[a]	0.62-0.78[a]	0.76[a]	0.67-0.86[a]
Cambodian	0.69[a]	0.48-0.99[a]	0.65[a]	0.45-0.96[a]
Chinese	1.39[a]	1.27-1.53[a]	1.58[a]	1.42-1.77[a]
Filipino	0.83[a]	0.72-0.95[a]	0.92	0.79-1.07
Hawai`ian/Pacific Islander	0.96	0.66-1.40	0.94	0.62-1.40
Hispanic	0.79[a]	0.74-0.85[a]	0.78[a]	0.72-0.84[a]
Japanese	1.33[a]	1.11-1.59[a]	1.41[a]	1.15-1.72[a]
Korean	1.43[a]	1.24-1.64[a]	1.45[a]	1.24-1.70[a]
Laotian/Hmong	0.24[a]	0.14-0.41[a]	0.30[a]	0.17-0.53[a]
Other Asian	1.38[a]	1.02-1.88[a]	1.27	0.91-1.78
South Asian	1.21	0.86-1.70	1.13	0.78-1.63
Thai	1.04	0.63-1.71	1.04	0.61-1.78
Vietnamese	1.34[a]	1.20-1.49[a]	1.26[a]	1.12-1.42[a]
White	1.00		1.00	
Age at diagnosis				
< 50			1.00	
50-59			0.83[a]	0.76-0.92[a]
60-69			0.76[a]	0.69-0.84[a]
70-79			0.47[a]	0.42-0.52[a]
⩾ 80			0.20[a]	0.17-0.24[a]
Gender				
Female			1.00	
Male			0.82[a]	0.77-0.88[a]
Socioeconomic Status				
1 - Low SES			1.00	
2			1.25[a]	1.13-1.37[a]
3			1.29[a]	1.17-1.42[a]
4			1.65[a]	1.49-1.82[a]
5 - High SES			1.84[a]	1.66-2.05[a]
Region				
Los Angeles			1.00	
San Francisco-Oakland			0.81[a]	0.74-0.88[a]
Central California			0.96	0.87-1.05
Northern California			1.09	0.98-1.20
San Diego-Imperial-Orange			1.34[a]	1.22-1.47[a]
Stage at diagnosis: 1988-1992				
Remote			1.00	
Regional			3.30[a]	2.29-4.75[a]
Local			8.28[a]	6.09-11.26[a]
Unstaged			0.27[a]	0.15-0.48[a]
Stage at diagnosis: 1993-1997				
Remote			1.00	
Regional			2.88[a]	2.02-4.11[a]
Local			8.81[a]	6.79-11.43[a]
Unstaged			0.47[a]	0.27-0.79[a]
Stage at diagnosis: 1998-2002				
Remote			1.00	
Regional			2.61[a]	2.01-3.40[a]
Local			8.07[a]	6.49-10.04[a]
Unstaged			0.78	0.52-1.17
Stage at diagnosis: 2003-2007				
Remote			1.00	
Regional			4.44[a]	3.44-5.73[a]
Local			12.97[a]	10.16-16.56[a]
Unstaged			0.93	0.58-1.49
Stage at diagnosis: 2008-2012				
Remote			1.00	
Regional			4.50[a]	3.43-5.92[a]
Local			13.6[a]	10.48-17.66[a]
Unstaged			1.12	0.68-1.87
Time period of diagnosis: remote stage tumors				

1988-1992	1.00	
1993-1997	0.75	0.53-1.06
1998-2002	0.89	0.64-1.23
2003-2007	0.83	0.58-1.17
2008-2012	0.59[a]	0.41-0.85[a]

[1]Adjusted for all other factors presented in the table using multivariable logistic regression. [a]$P < 0.05$. Time period X stage interaction $P = 0.0014$.

Table 3 Factors associated with survival from hepatocellular carcinoma in California, 1988-2012 (n = 33270)

	Cause-specific survival				All cause survival			
	Unadjusted HR	95%CI	Adjusted[1] HR	95%CI	Unadjusted HR	95%CI	Adjusted[1] HR	95%CI
American Indian/ Alaska Native	0.92	0.79-1.07	0.90	0.77-1.04	0.94	0.82-1.07	0.91	0.80-1.04
Black	1.12[a]	1.06-1.18[a]	1.07[a]	1.01-1.13[a]	1.12[a]	1.07-1.17[a]	1.06[a]	1.01-1.11[a]
Cambodian	1.38[a]	1.18-1.60[a]	1.35[a]	1.16-1.58[a]	1.31[a]	1.15-1.51[a]	1.27[a]	1.11-1.46[a]
Chinese	0.81[a]	0.77-0.86[a]	0.82[a]	0.77-0.86[a]	0.75[a]	0.72-0.79[a]	0.76[a]	0.72-0.79[a]
Filipino	0.95	0.88-1.01	0.84[a]	0.78-0.90[a]	0.98	0.92-1.04	0.88[a]	0.83-0.93[a]
Hawai`ian/ Pacific Islander	0.95	0.78-1.15	0.98	0.81-1.19	0.97	0.82-1.14	1.00	0.85-1.18
Hispanic	0.91[a]	0.88-0.95[a]	0.91[a]	0.88-0.94[a]	0.98	0.95-1.01	0.95[a]	0.92-0.99[a]
Japanese	0.95	0.86-1.04	0.93	0.84-1.02	0.88[a]	0.81-0.96[a]	0.86[a]	0.79-0.94[a]
Korean	0.87[a]	0.80-0.93[a]	0.90[a]	0.83-0.97[a]	0.80[a]	0.74-0.85[a]	0.82[a]	0.76-0.88[a]
Laotian/Hmong	1.91[a]	1.65-2.21[a]	1.50[a]	1.29-1.73[a]	1.74[a]	1.52-1.98[a]	1.37[a]	1.20-1.57[a]
Other Asian	0.80[a]	0.67-0.96[a]	0.98	0.82-1.17	0.80[a]	0.68-0.93[a]	0.96	0.82-1.12
South Asian	0.91	0.75-1.09	0.88	0.74-1.06	0.93	0.79-1.09	0.91	0.78-1.06
Thai	1.00	0.77-1.29	1.08	0.84-1.40	0.96	0.77-1.21	1.04	0.82-1.30
Vietnamese	0.83[a]	0.79-0.89[a]	0.85[a]	0.80-0.90[a]	0.79[a]	0.75-0.84[a]	0.80[a]	0.76-0.84[a]
White	1.00		1.00		1.00		1.00	
Age at diagnosis								
< 50			1.00				1.00	
50-59			1.01	0.96-1.06			1.04	1.00-1.09
60-69			1.06[a]	1.01-1.11[a]			1.08[a]	1.04-1.13[a]
70-79			1.29[a]	1.23-1.35[a]			1.29[a]	1.24-1.35[a]
≥ 80			1.54[a]	1.45-1.64[a]			1.57[a]	1.49-1.65[a]
Gender								
Female			1.00				1.00	
Male			1.10[a]	1.07-1.14[a]			1.09[a]	1.06-1.12[a]
Socioeconomic status								
1 - Low SES			1.00				1.00	
2			0.95[a]	0.92-0.99[a]			0.94[a]	0.91-0.98[a]
3			0.91[a]	0.88-0.95[a]			0.90[a]	0.87-0.94[a]
4			0.88[a]	0.84-0.92[a]			0.86[a]	0.83-0.89[a]
5 - High SES			0.81[a]	0.77-0.85[a]			0.79[a]	0.75-0.82[a]
Region								
Los Angeles			1.00				1.00	
San Francisco-Oakland			1.03	0.99-1.07			1.00	0.97-1.03
Central California			1.06[a]	1.02-1.11[a]			1.07[a]	1.03-1.11[a]
Northern California			1.14[a]	1.08-1.19[a]			1.08[a]	1.04-1.12[a]
San Diego-Imperial-Orange			1.09[a]	1.05-1.14[a]			1.08[a]	1.04-1.13[a]
Stage at diagnosis								
Remote			1.00				1.00	
Regional			0.70[a]	0.67-0.73[a]			0.71[a]	0.69-0.74[a]
Local			0.39[a]	0.38-0.41[a]			0.44[a]	0.43-0.46[a]
Unstaged			0.76[a]	0.72-0.79[a]			0.77[a]	0.74-0.80[a]
Time period of diagnosis								
1988-1992			1.00				1.00	
1993-1997			0.86[a]	0.82-0.91[a]			0.90[a]	0.86-0.95[a]

1998-2002	0.75[a]	0.71-0.79[a]	0.77[a]	0.74-0.81[a]
2003-2007	0.69[a]	0.66-0.73[a]	0.72[a]	0.68-0.75[a]
2008-2012	0.54[a]	0.51-0.57[a]	0.57[a]	0.54-0.60[a]
Type of surgery				
None	1.00		1.00	
Local	0.40[a]	0.38-0.43[a]	0.43[a]	0.41-0.46[a]
Resection or transplant	0.26[a]	0.25-0.28[a]	0.29[a]	0.28-0.31[a]

[1]Adjusted for all other factors presented in the table using Cox proportional hazards regression models. [a]$P < 0.05$.

DISCUSSION

We found substantial racial/ethnic variation in receipt of curative treatment, even after accounting for stage of disease and SES, which also varied considerably. These results are consistent with those of others[34], who also found that Blacks and Hispanics were less likely and Asians as a whole were more likely to receive treatment (although less likely to receive a transplant) than Whites. Patients with local stage disease were more likely to receive curative treatment than those with distant stage disease, and this advantage increased after changes to transplant guidelines in 2002 allowing for and increasing prioritization of transplantation in cases of local stage disease. Others have found that the change in guidelines did not lead to decreasing disparities in treatment[35].

We found that even after accounting for treatment differences, disparities in survival remained, with Blacks, Laotian/Hmong, and Cambodians experiencing significantly higher mortality than Whites, Hispanics, and most other Asian ethnicities. Those other Asian ethnic groups, such as Chinese and Vietnamese, have been the focus of longer histories of HBV screening than Blacks, Laotian/Hmong, and Cambodians and perhaps are the beneficiaries of earlier detection. Other studies have found Black-White differences to persist after adjustment for receipt of surgical treatment[19,22,36]. One study noted that even among transplant patients, Blacks had shorter and Asian/Pacific Islander patients had longer survival compared to Whites, with causes of death that suggested variation in the amount of immunosuppression accounted for differences in survival[19]. Consistent with others[37], we found that females had a survival advantage.

Differences in survival may be in part due to differences in comorbidities, stage of underlying liver disease, and etiology of HCC. A study using National Health and Nutrition Examination (NHANES) data found that risk factors for liver disease varied by race/ethnicity and gender, with Mexican Americans more likely than Blacks and Whites to have elevated aminotransferase activity, and Blacks more likely than Mexican Americans and Whites to have hepatitis B or C infection. Among men, Mexican Americans were more likely than Whites to be heavy/binge drinkers; among women, Mexican Americans and Blacks were more likely to be obese or diabetic but less likely to be heavy/binge drinkers than Whites[38]. Among East and Southeast Asians, HBV is the most common cause of HCC[1,20], except for Japanese, among whom HCV is more common[1]. HBV-associated HCC can occur without cirrhosis, which may confer a survival advantage as the typical complications of portal hypertension are not present[3].

HCC in the setting of a non-cirrhotic liver (NCL) is rare and has different etiologic, genetic, and pathologic characteristics from cirrhotic HCC, including a lower prevalence of HBV, HCV, and alcohol abuse, a lower rate of p53 mutation, and more advanced tumor stage at diagnosis[39]. Risk factors for the development of HCC in NCL include metabolic syndrome and non-alcoholic fatty liver disease, which may co-exist with viral hepatitis or alcohol abuse[40]. Hepatic resection is generally the best treatment choice for HCC patients with NCL, leading to better overall and disease-free survival than those of cirrhotic patients; in fact, survival after resection among NCL patients with non-advanced tumors is comparable to that of cirrhotic patients with early tumors who receive liver transplantation[39].

Compared to other etiologies, HCV-related HCC has been associated with poorer overall and recurrence-free survival after surgery[41]. Among patients with cirrhosis, those with chronic HCV experienced lower survival at 1, 3, and 5 years after liver transplantation compared to those without HCV. An accelerated progression to cirrhosis in HCV patients post-transplant may be responsible for this phenomenon seen in an era when treatment with interferon-based therapies was minimally effective in this population[42]. These outcomes will need to be revisited in the era of highly effective direct acting antiviral medications[41]. There is also evidence of racial differences in protein expression in HCV-associated HCC, indicating a possible biological mechanism for some disparities[43].

Other disparities in survival are likely due to differences in access to care and quality of treatment[18,36], as well as knowledge and attitudes regarding liver disease[44-46]. It is clear that gaps in both patient and provider knowledge lead to decreased screening and vaccination rates among those at risk for chronic hepatitis B[47-51]. Trends in earlier stage at diagnosis and leveling off of liver cancer incidence rates among Asians as a whole have been attributed to HBV testing and surveillance of those chronically infected[3,21]. Now that

all-oral, curative treatment for HCV is available, HCV testing of people born in 1945-1965 is recommended[52]. Nevertheless, barriers to HBV and HCV testing and treatment remain[21,53-55]. However, attempts to intentionally link HBV screening results with linkage to care, while not optimized yet, are promising[56].

In summary, this paper reports on and analyzes 33270 HCC cases among Californians who were diagnosed over a 25-year period from 1988 to 2012. To our knowledge, these data represent the largest and most racially/ethnic diverse study of HCC cases collected through a registry with a Gold Certification (highest award) from the North American Association of Central Cancer Registries. Previously published reports of HCC cases utilizing the California Cancer Registry were focused on specific population groups, *e.g.,* Asian Americans[23] or combined analyses of two population groups, *e.g.,* Asian Americans and Hispanics[57] or were otherwise limited in numbers of cases, geographic scope, time period. Papers utilizing the SEER cancer registries, including those in California, were limited to a focus on a single racial category, *e.g.,* American Indians and Alaska Natives[58] or did not analyze as many disaggregated ethnic groups. Our findings underscore the need for disaggregation-those least likely to be treated and those with the highest mortality were Asian, as were those most likely to be treated and those with the lowest mortality. Our analyses provided greater granularity by including as separate categories: Cambodian, Chinese, Filipino, Hawai`ian/Pacific Islander, Japanese, Korean, Laotian/Hmong, Other Asian, South Asian, Thai, and Vietnamese, almost all of whom are at higher risk for HCC compared to the population-at-large. The greater granularity also enabled us to specifically identify populations-at-risk who share common socio-ethnic characteristics. Thus, the findings from this paper offer the potential for more precise targeting of interventions by ethnic group, and hence language preference, and geographical area.

Despite the advantages of being able to access and analyze the largest cancer registry in a geographically contiguous political jurisdiction, we recognize several limitations. We were not able to assess racial/ethnic differences in receipt of transplant over this time period because the CCR did not distinguish between transplant and resection until 1998. The CCR does not include data on risk factors, such as exposure to viral infections, cirrhosis, alcohol consumption, or documentation of an individual's metabolic syndrome/diabetes or body mass index as a measure of obesity. These latter risk factors are increasingly influential in HCC etiology[11]. No data are captured regarding the patients' English fluency or other potential measures of acculturation and access to care. The aggregate socioeconomic status variables are not measures of the individual patients but rather that of their Census block group[31,32]. Although the CCR employs extensive follow-up procedures it is possible that some patients returned to their home countries to die[59]. Finally, there was limited power to detect treatment and survival differences for racial/ethnic groups with small numbers of cases.

In conclusion, nonetheless these findings demonstrate substantial racial/ethnic disparities in HCC treatment and survival that were not explained by disease stage, time period of diagnosis, or socio-demographic factors. Continued effort is required to improve access and attitudes towards HBV and HCV testing and follow-up, address other etiological risk factors such as alcoholism and obesity, develop targeted therapies, and provide high quality treatment to all patients.

COMMENTS

Background

Cancer of the liver and intrahepatic bile duct, of which approximately 80% is hepatocellular carcinoma (HCC), led the 17 most common cancer sites with a 3.1% average annual increase in mortality rates between 2008 and 2012 among both men and women in the United States.

Research frontiers

The authors' previous study of more than 6000 HCC cases diagnosed in California in 1988-2007, which reported on specific Asian ethnicities, found substantial inter-ethnic variation in survival but did not include comparison with other racial/ethnic groups. Rarely have HCC survival and treatment characteristics been characterized for 15 race/ethnic groups in a large geographically contiguous area over a period of 25 years.

Innovations and breakthroughs

This paper reports on and analyzes 33270 HCC cases among Californians who were diagnosed over a 25-year period from 1988 to 2012. To the best knowledge of the authors, these data represent the largest and most racially/ethnic diverse study of HCC cases collected through a Gold Certification (highest award) North American Association of Central Cancer Registries.

Applications

Nonetheless these findings demonstrate substantial racial/ethnic disparities in HCC treatment and survival that were not explained by disease stage, time period of diagnosis, or socio-demographic factors.

Peer-review

Non-cirrhotic liver with HCC has a different prognosis from a liver cirrhosis and HCV-related cirrhosis has a different survival rates in comparison to other etiologies.

ACKNOWLEDGMENTS

The production of this paper was supported in part by a cooperative agreement from the National Cancer Institute, U54CA153499, but the views of this paper are those of the authors and not necessarily those of the National Cancer Institute.

REFERENCES

1 **Zhu RX**, Seto WK, Lai CL, Yuen MF. Epidemiology of Hepatocellular Carcinoma in the Asia-Pacific Region. *Gut Liver* 2016; **10**: 332-339 [PMID: 27114433 DOI: 10.5009/gnl15257]

2 **Ryerson AB**, Eheman CR, Altekruse SF, Ward JW, Jemal A, Sherman RL, Henley SJ, Holtzman D, Lake A, Noone AM, Anderson RN, Ma J, Ly KN, Cronin KA, Penberthy L, Kohler BA. Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. *Cancer* 2016; **122**: 1312-1337 [PMID: 26959385 DOI: 10.1002/cncr.29936]

3 **Njei B**, Rotman Y, Ditah I, Lim JK. Emerging trends in hepatocellular carcinoma incidence and mortality. *Hepatology* 2015; **61**: 191-199 [PMID: 25142309 DOI: 10.1002/hep.27388]

4 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]

5 **El-Serag HB**. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012; **142**: 1264-1273.e1 [PMID: 22537432 DOI: 10.1053/j.gastro.2011.12.061]

6 **Kuper H**, Adami HO, Trichopoulos D. Infections as a major preventable cause of human cancer. *J Intern Med* 2000; **248**: 171-183 [PMID: 10971784]

7 **Chen MS Jr**, Dang J. Hepatitis B among Asian Americans: Prevalence, progress, and prospects for control. *World J Gastroenterol* 2015; **21**: 11924-11930 [PMID: 26576081 DOI: 10.3748/wjg.v21.i42.11924]

8 **El-Serag HB**. Hepatocellular carcinoma. *N Engl J Med* 2011; **365**: 1118-1127 [PMID: 21992124 DOI: 10.1056/NEJMra1001683]

9 **El-Serag HB**, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clin Gastroenterol Hepatol* 2006; **4**: 369-380 [PMID: 16527702 DOI: 10.1016/j.cgh.2005.12.007]

10 **El-Serag HB**, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 2004; **126**: 460-468 [PMID: 14762783]

11 **Waller LP**, Deshpande V, Pyrsopoulos N. Hepatocellular carcinoma: A comprehensive review. *World J Hepatol* 2015; **7**: 2648-2663 [PMID: 26609342 DOI: 10.4254/wjh.v7.i26.2648]

12 **Altekruse SF**, Henley SJ, Cucinelli JE, McGlynn KA. Changing hepatocellular carcinoma incidence and liver cancer mortality rates in the United States. *Am J Gastroenterol* 2014; **109**: 542-553 [PMID: 24513805 DOI: 10.1038/ajg.2014.11]

13 **Smith BD**, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol* 2009; **27**: 2758-2765 [PMID: 19403886 DOI: 10.1200/JCO.2008.20.8983]

14 **Petrick JL**, Kelly SP, Altekruse SF, McGlynn KA, Rosenberg PS. Future of Hepatocellular Carcinoma Incidence in the United States Forecast Through 2030. *J Clin Oncol* 2016; **34**: 1787-1794 [PMID: 27044939 DOI: 10.1200/JCO.2015.64.7412]

15 **Chen MS Jr**. Preventing Hepatitis B-induced Liver Cancer: Implications for Eliminating Health Disparities. *J Health Dispar Res Pract* 2010; **4**: 88-99 [PMID: 21785754]

16 **Howlader N**, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2013. National Cancer Institute: Surveillance, Epidemiology, and End Results Program 2016. Available from: URL: http://seer.cancer.gov/csr/1975_2013/

17 **Rodriguez DN**, Torruellas C, Cress RD. Trends in early-stage hepatocellular carcinoma, California 1988-2010. *Cancer Causes Control* 2016; **27**: 325-331 [PMID: 26662039 DOI: 10.1007/s10552-015-0705-2]

18 **Harlan LC**, Parsons HM, Wiggins CL, Stevens JL, Patt YZ. Treatment of hepatocellular carcinoma in the community: disparities in standard therapy. *Liver Cancer* 2015; **4**: 70-83 [PMID: 26020030 DOI: 10.1159/000367729]

19 **Njei B**, Ditah I, Lim JK. Persistent racial disparities in survival among u.s. Adults with hepatocellular carcinoma after liver transplantation: the paradox of all-cause and cause-specific mortality. *Gastrointest Cancer Res* 2013; **6**: 73-74 [PMID: 23936546]

20 **Wong RJ**, Corley DA. Survival differences by race/ethnicity and treatment for localized hepatocellular carcinoma within the United States. *Dig Dis Sci* 2009; **54**: 2031-2039 [PMID: 19117131 DOI: 10.1007/s10620-008-0661-8]

21 **Ha J**, Yan M, Aguilar M, Bhuket T, Tana MM, Liu B, Gish RG, Wong RJ. Race/ethnicity-specific disparities in cancer incidence, burden of disease, and overall survival among patients with hepatocellular carcinoma in the United States. *Cancer* 2016; **122**: 2512-2523 [PMID: 27195481 DOI: 10.1002/cncr.30103]

22 **Sloane D**, Chen H, Howell C. Racial disparity in primary hepatocellular carcinoma: tumor stage at presentation, surgical treatment and survival. *J Natl Med Assoc* 2006; **98**: 1934-1939 [PMID: 17225837]

23 **Kwong SL**, Stewart SL, Aoki CA, Chen MS Jr. Disparities in hepatocellular carcinoma survival among Californians of Asian ancestry, 1988 to 2007. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 2747-2757 [PMID: 20823106 DOI: 10.1158/1055-9965.EPI-10-0477]

24 **Kwong SL**, Chen MS Jr, Snipes KP, Bal DG, Wright WE. Asian subgroups and cancer incidence and mortality rates in California. *Cancer* 2005; **104**: 2975-2981 [PMID: 16247792 DOI: 10.1002/cncr.21511]

25 **NAACCR Race and Ethnicity Work Group**. NAACCR Asian Pacific Islander identification algorithm (NAPIIA v1.2.1). Springfield, IL: North American Association of Central Cancer Registries, 2011

26 **NAACCR Race and Ethnicity Work Group**. NAACCR guideline for enhancing Hispanic/Latino identification: revised NAACR Hispanic/Latino identification algorithm (NHIA v2.2.1). Springfield, IL: North American Association of Central Cancer Registries, 2011

27 **Fang DM**, Lee S, Stewart S, Ly MY, Chen MS Jr. Factors associated with pap testing among Hmong women. *J Health Care Poor Underserved* 2010; **21**: 839-850 [PMID: 20693730 DOI: 10.1353/hpu.0.0338]

28 **Yang RC**, Mills PK, Riordan DG. Cervical cancer among Hmong women in California, 1988 to 2000. *Am J Prev Med* 2004; **27**: 132-138 [PMID: 15261900 DOI: 10.1016/j.amepre.2004.04.003]

29 **Shankar LD**, Srikanth R. A Part, Yet Apart. South Asians in Asian America: Temple University Press, 1998

30 **Parikh-Patel A**, Mills PK, Jain RV. Breast cancer survival among South Asian women in California (United States). *Cancer Causes Control* 2006; **17**: 267-272 [PMID: 16489534 DOI: 10.1007/s10552-005-0520-2]

31 **Yost K**, Perkins C, Cohen R, Morris C, Wright W. Socioeconomic status and breast cancer incidence in California for different race/ethnic groups. *Cancer Causes Control* 2001; **12**: 703-711 [PMID: 11562110]

32 **Yang J**, Schupp CW, Harrati A Clark C, Keegan THM, Gomez SL. Developing an area-based socioeconomic measure from American Community Survey data. Fremont, California: Cancer Prevention Institute of California, 2014

33 **Robbins AS**, Daily MF, Aoki CA, Chen MS Jr, Troppmann C, Perez RV. Decreasing disparity in liver transplantation among white and Asian patients with hepatocellular carcinoma: California, 1998-2005. *Cancer* 2008; **113**: 2173-2179 [PMID: 18792066 DOI: 10.1002/cncr.23766]

34 **Ha J**, Yan M, Aguilar M, Tana M, Liu B, Frenette CT, Bhuket T, Wong RJ. Race/Ethnicity-specific Disparities in Hepatocellular Carcinoma Stage at Diagnosis and its Impact on Receipt of Curative Therapies. *J Clin Gastroenterol* 2016; **50**: 423-430 [PMID: 26583267 DOI: 10.1097/MCG.0000000000000448]

35 **Robbins AS**, Cox DD, Johnson LB, Ward EM. Persistent disparities in liver transplantation for patients with hepatocellular carcinoma in the United States, 1998 through 2007. *Cancer* 2011; **117**: 4531-4539 [PMID: 21448933 DOI: 10.1002/cncr.26063]

36 **Mathur AK**, Osborne NH, Lynch RJ, Ghaferi AA, Dimick JB, Sonnenday CJ. Racial/ethnic disparities in access to care and survival for patients with early-stage hepatocellular carcinoma. *Arch Surg* 2010; **145**: 1158-1163 [PMID: 21173289 DOI: 10.1001/archsurg.2010.272]

37 **Dohmen K**, Shigematsu H, Irie K, Ishibashi H. Longer survival in female than male with hepatocellular carcinoma. *J Gastroenterol Hepatol* 2003; **18**: 267-272 [PMID: 12603526]

38 **Flores YN**, Yee HF, Leng M, Escarce JJ, Bastani R, Salmerón J, Morales LS. Risk factors for chronic liver disease in Blacks, Mexican Americans, and Whites in the United States: results from NHANES IV, 1999-2004. *Am J Gastroenterol* 2008; **103**: 2231-2238 [PMID: 18671818 DOI: 10.1111/j.1572-0241.2008.02022.x]

39 **Trevisani F**, Frigerio M, Santi V, Grignaschi A, Bernardi M. Hepatocellular carcinoma in non-cirrhotic liver: a reappraisal. *Dig Liver Dis* 2010; **42**: 341-347 [PMID: 19828388 DOI: 10.1016/j.dld.2009.09.002]

40 **Schütte K**, Schulz C, Poranzke J, Antweiler K, Bornschein J, Bretschneider T, Arend J, Ricke J, Malfertheiner P. Characterization and prognosis of patients with hepatocellular carcinoma (HCC) in the non-cirrhotic liver. *BMC Gastroenterol* 2014; **14**: 117 [PMID: 24990270 DOI: 10.1186/1471-230X-14-117]

41 **Shindoh J**, Hashimoto M, Watanabe G. Surgical approach for hepatitis C virus-related hepatocellular carcinoma. *World J Hepatol* 2015; **7**: 70-77 [PMID: 25624998 DOI: 10.4254/wjh.v7.i1.70]

42 **Bozorgzadeh A**, Orloff M, Abt P, Tsoulfas G, Younan D, Kashyap R, Jain A, Mantry P, Maliakkal B, Khorana A, Schwartz S. Survival outcomes in liver transplantation for hepatocellular carcinoma, comparing impact of hepatitis C versus other etiology of cirrhosis. *Liver Transpl* 2007; **13**: 807-813 [PMID: 17539001 DOI: 10.1002/lt.21054]

43 **Dillon ST**, Bhasin MK, Feng X, Koh DW, Daoud SS. Quantitative proteomic analysis in HCV-induced HCC reveals sets of proteins with potential significance for racial disparity. *J Transl Med* 2013; **11**: 239 [PMID: 24283668 DOI: 10.1186/1479-5876-11-239]

44 **Maxwell AE**, Stewart SL, Glenn BA, Wong WK, Yasui Y, Chang LC, Taylor VM, Nguyen TT, Chen MS Jr, Bastani R. Theoretically informed correlates of hepatitis B knowledge among four Asian groups: the health behavior framework. *Asian Pac J Cancer Prev* 2012; **13**: 1687-1692 [PMID: 22799389 DOI: 10.1007/s11606-010-1285-1]

45 **Burnham B**, Wallington S, Jillson IA, Trandafili H, Shetty K, Wang J, Loffredo CA. Knowledge, attitudes, and beliefs of patients with chronic liver disease. *Am J Health Behav* 2014; **38**: 737-744 [PMID: 24933143 DOI: 10.5993/AJHB.38.5.11]

46 **Safo SA**, Batchelder A, Peyser D, Litwin AH. The common sense model applied to hepatitis C: a qualitative analysis of the impact of disease comparison and witnessed death on hepatitis C illness perception. *Harm Reduct J* 2015; **12**: 20 [PMID: 26092261 DOI: 10.1186/s12954-015-0054-1]

47 **Chen H**, Tu SP, Teh CZ, Yip MP, Choe JH, Hislop TG, Taylor VM, Thompson B. Lay beliefs about hepatitis among North American Chinese: implications for hepatitis prevention. *J Community Health* 2006; **31**: 94-112 [PMID: 16737171]

48 **Wu CA**, Lin SY, So SK, Chang ET. Hepatitis B and liver cancer knowledge and preventive practices among Asian Americans in the San Francisco Bay Area, California. *Asian Pac J Cancer Prev* 2007; **8**: 127-134 [PMID: 17477787]

49 **Chao SD**, Wang BM, Chang ET, Ma L, So SK. Medical training fails to prepare providers to care for patients with chronic hepatitis B infection. *World J Gastroenterol* 2015; **21**: 6914-6923 [PMID: 26078568 DOI: 10.3748/wjg.v21.i22.6914]

50 **Robotin M**, Patton Y, George J. Getting it right: the impact of a continuing medical education program on hepatitis B knowledge of Australian primary care providers. *Int J Gen Med* 2013; **6**: 115-122 [PMID: 23662074 DOI: 10.2147/IJGM.S41299]

51 **Upadhyaya N**, Chang R, Davis C, Conti MC, Salinas-Garcia D, Tang H. Chronic hepatitis B: perceptions in Asian American communities and diagnosis and management practices among primary care physicians. *Postgrad Med* 2010; **122**: 165-175 [PMID: 20861600 DOI: 10.3810/pgm.2010.09.2213]

52 **Smith BD**, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Teo CG, Jewett A, Baack B, Rein DB, Patel N, Alter M, Yartel A, Ward JW. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR Recomm Rep* 2012; **61**: 1-32 [PMID: 22895429]

53 **Zeremski M**, Zibbell JE, Martinez AD, Kritz S, Smith BD, Talal AH. Hepatitis C virus control among persons who inject drugs requires overcoming barriers to care. *World J Gastroenterol* 2013; **19**: 7846-7851 [PMID: 24307778 DOI: 10.3748/wjg.v19.i44.7846]

54 **Ha NB**, Trinh HN, Nguyen TT, Leduc TS, Bui C, Ha NB, Wong CR, Tran AT, Nguyen MH. Prevalence, risk factors, and disease knowledge of chronic hepatitis B infection in Vietnamese Americans in California. *J Cancer Educ* 2013; **28**: 319-324 [PMID: 23564428 DOI: 10.1007/s13187-013-0466-0]

55 **Ditah I**, Al Bawardy B, Gonzalez HC, Saberi B, Ditah C, Kamath PS, Charlton M. Lack of health insurance limits the benefits of hepatitis C virus screening: insights from the National Health and Nutrition Examination Hepatitis C follow-up study. *Am J Gastroenterol* 2015; **110**: 1126-1133 [PMID: 25756239 DOI: 10.1038/ajg.2015.31]

56 **Dang JH**, Chen MS Jr. Increasing Hepatitis B Testing and Linkage to Care of Foreign-Born Asians, Sacramento, California, 2012-2013. *Public Health Rep* 2016; **131** Suppl 2: 119-124 [PMID: 27168671]

57 **Chang ET**, Yang J, Alfaro-Velcamp T, So SK, Glaser SL, Gomez SL. Disparities in liver cancer incidence by nativity, acculturation, and socioeconomic status in California Hispanics and Asians. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 3106-3118 [PMID: 20940276 DOI: 10.1158/1055-9965.EPI-10-0863]

58 **Jim MA**, Perdue DG, Richardson LC, Espey DK, Redd JT, Martin HJ, Kwong SL, Kelly JJ, Henderson JA, Ahmed F. Primary liver cancer incidence among American Indians and Alaska Natives, US, 1999-2004. *Cancer* 2008; **113**: 1244-1255 [PMID: 18720380 DOI: 10.1002/cncr.23728]

59 **Gomez SL**, Clarke CA, Shema SJ, Chang ET, Keegan TH, Glaser SL. Disparities in breast cancer survival among Asian women by ethnicity and immigrant status: a population-based study. *Am J Public Health* 2010; **100**: 861-869 [PMID: 20299648 DOI: 10.2105/AJPH.2009.176651]

P- Reviewer: Santambrogio R **S- Editor**: Qi Y **L- Editor**: A
E- Editor: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327